CROSS-REFERENCE TO RELATED APPLICATION

The above-identified application claims priority from U.S. Application Nos. 09/177,776 and 09/178,115, both of which were filed on October 23, 1998. Application 09/177,776 has since issued as U.S. Patent No. 6,297,051.

REMARKS

The Specification has been amended to correct a number of typographical/proofreading errors. For example, the Specification at page 18 has been amended to correct a typographical/proofreading error in the abbreviation of "kilodalton," from "kDA" to "kDa."

Claim 31 has been amended to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention. The nucleic acid coding sequence for the MN protein has been incorporated into Claim 31, for purposes of increased clarity and particularity. Support for the description of the MN protein in relation to the MN cDNA sequence can be found at least at page 19, lines 9-13 and at page 22, line 22 to page 24, line 2.

Support for the additional method steps for amended Claim 31 can be found at the least at page 57, lines 9-23; at page 60, line 29 to page 61, line 3; at page 62, lines 18-26; at page 63, line 28 to page 64, line 10; at page 65, line 26 to page 66, line 4; at page 67, lines 28-30; and at page 68, lines 15-20.

Applicants respectfully conclude that the above amendments do not introduce any new matter.

Claims 31-42 are now pending and under examination. Applicants respectfully request entry of the above amendments and reconsideration of the application as amended.

35 U.S.C. Section 112, Second Paragraph Rejection

Claims 31-42 stand rejected under 35 U.S.C. Section 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." [Office Action, page 2, section 4.] Applicants respectfully traverse and request that the Examiner reconsider and withdraw the rejection in view of the amendments to the claim 31 and the following remarks.

The Office Action at page 2, section 5, states: "Regarding claims 31-42 in the recitation of the term 'MN protein,' the abbreviation of the protein name must be accompanied by the full name of the protein."

Applicants respectfully submit that the term "MN protein" complies with the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully point out that Claim 31 has been amended to recite, in part:

> . . . wherein said MN protein is encoded by a nucleic acid whose nucleotide sequence is selected from the group consisting of:
>
> (1) SEQ ID NO: 1;

(2) nucleotide sequences that hybridize specifically under stringent hybridization conditions to the complement of SEQ ID NO: 1; and

(3) nucleotide sequences that differ from SEQ ID NO: 1 or from the nucleotide sequences of (2) in codon sequence due to the degeneracy of the genetic code.

[Claim 31, as amended.]

For historic reasons, "MN protein" stands for the somewhat unwieldy term "endogenous component of the MaTu protein," in contrast to "MX protein," or "exogenous component of the MaTu protein." However, the term "MN protein" has come into usage and is the term by which the protein is now known in the art. The term "MN protein" is defined in the specification, at least at pages 1, lines 5-9, in the Background of the Invention as well as in relation to the MN cDNA, for example, at page 19, lines 9-13 and at page 22, line 22 to page 24, line 2.

Furthermore, Applicants respectfully point out that the term "MN protein" is well-known to those in the art; there are over eighteen publications in the recent peer-reviewed literature using that term. A list of these publications is provided as an attachment to this response, identified as Appendix A. Applicants therefore respectfully submit that the term "MN protein" complies with the requirements of 35 U.S.C. § 112, second paragraph.

The Office Action further states that

regarding claim 31, 38, 39, 40 and dependent claims thereof in the recitation of the term

> "site", it is unclear from the specification as to which site is being referred. Furthermore, because it is not known where amongst the MN protein the identified molecule is to bind, the metes and bounds of the term cannot be determined.

[Office Action, page 2, section 6.]

The site on a MN protein is further described in the instant application as:

> The site on MN proteins to which vertebrate cells adhere in said cell adhesion assay is preferably within the proteoglycan-like domain [SEQ ID NO: 50] or within the carbonic anhydrase domain [SEQ ID NO: 51] of the MN protein. Preferably that site comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 and 97-106. Still further preferably, that site has an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 and 97-106. site

[Instant application, page 7, lines 18-23.]

Applicants respectfully submit that ones of skill in the art have been given very specific direction by the Specification of the instant application, for the site on the MN protein "to which vertebrate cells adhere in a cell adhesion assay," and that the metes and bounds of that term can in fact be determined. Therefore, Applicants respectfully submit that the term "site" complies with the requirements of 35 U.S.C. § 112, second paragraph.

Additionally, the Office Action states that "(r)egarding claim 31 and dependent claims thereof, it is not clear as to how the determination of molecules that bind to the

'site' is to be determined because the necessary method steps have not been recited." [Office Action, page 3, Section 7.]

Applicants respectfully point out that independent Claim 31 has now been amended to include method steps for the determination of molecules that bind to the "site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay." Claim 31 has now been amended to read, in part

> 31. A method of identifying an organic or an inorganic molecule that binds specifically to a site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay, comprising testing organic or inorganic molecules in a cell adhesion assay, comprising:
>
> (a) allowing said MN protein to bind to a substrate, to which cells do not bind;
>
> (b) rinsing unbound MN protein from said substrate;
>
> (c) incubating said bound MN protein with said organic or inorganic molecules, and with said vertebrate cells;
>
> (d) rinsing unbound vertebrate cells from said MN protein; and
>
> (e) identifying molecules that inhibit the adhesion of said vertebrate cells to said MN protein as specifically binding to said site . . .

Applicants respectfully submit that claim 31 as amended is clear as to how the determination of molecules that bind to the "site" is to be determined, because the necessary method steps have been recited.

Furthermore, the Specification of the application of the present invention sets forth how to perform adhesion assays, and cites to articles describing the cell adhesion assay, which is well-known in the art; for example, at page 21, lines 13-14 [Pierschbacher and Ruoslahti PNAS 81:5985 (1984); Ruoslahti and Pierschbacher, Science 238:491.]; and at page 57, lines 10-12 [Hoffman S., "Assays of cell adhesion," IN: Cell-cell Interactions, (Stevenson et al. eds.) pp. 1-30 (IRL Press at Oxford University Press; Oxford, N.Y., Tokyo; 1992)].

Further, the Specification describes the novel method of using cell adhesion inhibition assays to test for molecules that inhibit cell binding to MN protein at least at page 57, lines 9-23; at page 60, line 29 to page 61, line 31 (Example 1); and at page 62, line 10 to page 70, line 14 (Example 2). The Specification also provides examples of how to identify peptides that bind to MN protein using a commercially available phage display library (See Examples 2 and 3, wherein a Ph.D.® -7 Peptide 7-mer Library Kit from New England Biolabs, a representative phage display library, is used.)

Therefore, Applicants respectfully submit that amended claim 31 complies with the requirements of 35 U.S.C. § 112, second paragraph.

At page 3, Section 8, the Office Action states: "Regarding claim 37 in the recitation of the phrase 'abnormally expressed', it is considered a relative term of which the metes

and bounds cannot be determined. To what extent of normal expression would normal become abnormal expression."

Applicants respectfully traverse, and submit that in the specific case of the MN protein, "abnormal expression" does not refer to subtle changes in MN protein expression, but to the unexpected presence or absence of MN protein expression, or to extreme changes in MN protein expression. As the Specification explains at page 1, lines 19-23, the MN protein

> . . . is found in many types of human carcinomas (notably uterine cervical, ovarian, endometrial, renal, bladder, breast, colorectal, lung, esophageal, and prostate, among others). Very few normal tissues have been found to express MN protein to any significant degree. Those MN-expressing normal tissues include the human gastric mucosa and gallbladder epithelium, and some other normal tissues of the alimentary tract.

[Emphasis added.]

The Specification continues at page 1:

> In general, oncogenesis may be signified by the abnormal expression of MN protein. For example, oncogenesis may be signified: (1) when MN protein is present in a tissue which normally does not express MN protein to any significant degree; (2)when MN protein is absent from a tissue that normally expresses it; (3)when MN gene expression is at a significantly increased level, or at a significantly reduced level from that normally expressed in a tissue; or (4)when MN protein is expressed in an abnormal location within a cell.

[Instant application, page 1, line 28, to page 2, line 2; emphasis added.]

Applicants respectfully submit that the Specification clearly teaches one of skill in the art how to determine "abnormal expression" of MN protein, and that claim 37 complies with the requirements of 35 U.S.C. § 112, second paragraph.

The Office Action at page 3, section 9, states:

> (r)egarding claim 31, 33, 37, and dependent claims thereof in the recitation of the term "inorganic molecule", it is unclear from the specification as to the metes and bounds of the term. Although it is understood in general what the term is to mean, there are many types of inorganic molecules of which can be encompassed by this term.

Applicants respectfully submit that the term "inorganic molecule" is well-known to those of skill in the art. The Examiner even conceded that it is understood in general what the term "inorganic molecules" means. Therefore, the term is not indefinite.

Further, the present invention describes a method of screening potentially therapeutic molecules, both organic and inorganic, for a desirable property, namely the ability to prevent cells from binding to MN protein, which property can be useful in the therapy of neoplastic disease. As described in the present application,

> Computer modeling can also be used to design molecules with specific affinity to MN protein that would mediate steric inhibition between MN protein and its receptor. A computer model of the MN binding site for the receptor will contain spatial, electrostatic, hydrophobic and other characteristics of this

> structure. Organic molecules complementary to the structure, that best fit into the binding site, will be designed. Inorganic molecules can also be similarly tested that could block the MN binding site.

[Instant Application, page 21, line 31 to page 22, line 5; emphasis added.]

Therefore, in selecting suitable candidate inorganic molecules to be tested for inhibition of MN protein binding to cells, preference would be given to those inorganic molecules that, according to computer modeling, could fit into the MN binding site.

Since the method of the present invention is a screening assay, it is not yet known which of all the potential candidate molecules can be useful therapeutically until they are subjected to the test provided by the present invention. Applicants respectfully point out that the term is not indefinite, and therefore Applicants are entitled to a claim of sufficient scope to cover all the claimed types of candidate molecules to be screened.

Applicants respectfully submit that the pending claims comply with the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that the Examiner withdraw the rejections.

35 U.S.C. Section 102 Rejection

Claims 31, 32, 37, 38, 39, 40, 41, 42 stand "rejected under 35 U.S.C. 102(b) as being anticipated by Zavada *et al* (Int. J. Oncology 1997, 10(4):857-863)." [Office Action, page 3, Section 11.] The Office Action further states at page 4, "Zavada *et al* teach the identification of an antibody to MN protein which is used to inhibit the binding of human derived cells in a cell adhesion assay. The antibody identified corresponds to an epitope that is located either in the proteoglycan domain or in the carbonic anhydrase domain." Applicants respectfully traverse this rejection.

In order to serve as an anticipating reference, a reference must teach each and every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Zavada et al. 1997 reference does not teach each and every step of the pending claims, and thus is not effective prior art, and cannot serve as an anticipating reference. Zavada *et al.* is not an anticipating reference because it did not disclose or suggest the use of a cell adhesion assay in a method for "identifying an organic or inorganic molecule that binds specifically to a site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay," as required by Claim 31.

The 1997 Zavada et al. reference primarily described transient transfection of mammalian cells by MN protein, which resulted in temporary morphologic transformation of the cells. The cell adhesion assays performed were directed to determining whether or not MN protein is a CAM, or cell adhesion molecule, and not to their use as a screening assay. In fact, while according to Zavada et al. "NIH3T3 cells adhered, spread and grew on patches of adsorbed MN protein", prior addition of MN-specific antibody to adsorbed MN protein did not prevent the binding of NIH3T3 cells: "Blocking of adsorbed MN protein with an excess of Mab M75 did not abrogate the adhesion of NIH3T3 cells." [Zavada et al. page 861, column 1, first full paragraph, to end of column 1; emphasis added.] Instead, in order to demonstrate MN specificity the MN protein was first 1) absorbed with Staphylococcus aureus cells (SAC) loaded with M75 antibody, 2) before being bound to the substrate, as follows:

> To confirm the specificity of adhesion, MN protein was absorbed with SAC loaded with MAb M75 (directed to MN) or MAb M67, directed to an unrelated antigen (Pastorekova et al., Virology 187:620-626, 1992), before it was applied to the surface of the Petri dishes. Absorption with the SAC-M75 complex totally abrogated the cell binding activity, whereas absorption with SAC-M67 was without any effect.
>
> [Zavada et al., 1997, page 861, top of column 2; emphasis added.]

Applicants respectfully point out that the method steps of the present invention do not require the prior formation of complexes between the "organic molecules" of independent Claim 31 with any other molecules or bacterial cells such as SAC, nor the absorption of MN protein to such complexes, prior to testing for inhibition of vertebrate cell binding to MN protein.

As amended, Claim 31 recites, in part:

> 31. A method of identifying an organic or an inorganic molecule that binds specifically to a site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay, comprising testing organic or inorganic molecules in a cell adhesion assay, comprising:
>
> (a) allowing said MN protein to bind to a substrate, to which cells do not bind;
>
> (b) rinsing unbound MN protein from said substrate;
>
> (c) incubating said bound MN protein with said organic or inorganic molecules, and with said vertebrate cells;
>
> (d) rinsing unbound vertebrate cells from said MN protein; and
>
> (e) identifying molecules that inhibit the adhesion of said vertebrate cells to said MN protein as specifically binding to said site . . .

As recited in amended Claim 31, the methods of the present invention teach that the MN protein is first bound to the substrate, before the addition of any organic or inorganic molecules to be screened for inhibition of vertebrate cell binding to MN protein.

Further, according to the Zavada *et al.* reference, the antibody to MN protein by itself did not inhibit the binding of vertebrate cells to MN protein. In order to serve as an anticipating reference, the cited art must provide an enabling disclosure teaching one skilled in the art to practice the claimed invention. "To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." PPG Industries, Inc. v. Guardian Industries Corp., 37 USPQ2d 1618 (Fed. Cir. 1996); "The disclosure must be enabling such that it 'describe[s] the [inventor's] claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." Synbiotics Corp. v. Heska Corp, 59 USPQ2d 1329, 1336 (S. D. Cal. 2000) quoting In re Paulsen, 31 USPQ2d 1671 (Fed. Cir. 1994). As explained above, Zavada et al. teach that prior addition of MN-specific antibody to adsorbed MN protein did not prevent the binding of NIH3T3 cells: "Blocking of adsorbed MN protein with an excess of Mab M75 did not abrogate the adhesion of NIH3T3 cells." [Zavada et al. page 861, column 1, first full paragraph, to end of column 1; emphasis added.] Therefore, for this additional reason, Zavada *et al.* is not effective prior art and cannot serve as an anticipating reference against the methods of the pending claims.

Therefore Applicants respectfully submit that the rejection of claims 31, 32, 37, 38, 39, 40, 41, 42 under 35

U.S.C. 102(b) as being anticipated by Zavada et al. has been overcome and request that the rejection be withdrawn.

35 U.S.C. Section 102 Rejection

Claims 31, 32, 34-42 stand "rejected under 35 U.S.C. 102(b) as being anticipated by Zavada *et al* (WO 95/34650)." [Office Action, page 4, Section 12.] The Office Action further states at page 4: "Zavada *et al* teach a method of identifying peptides and antibodies that bind to the MN protein within either the carbonic anhydrase domain or within the proteoglycan domain, which is represented by SEQ ID No: 10 and 97-106 or 107-109 and 137-138. The claims are therefore anticipated."

Applicants respectfully traverse this rejection, and respectfully submit that Zavada *et al*. do not teach each and every element of claims 31, 32, and 34-42, as required for an anticipating reference. Therefore Zavada et al. (WO 95/34650) cannot anticipate the pending claims.

As recited above, claim 31 is directed to "a method of identifying an organic or inorganic molecule that binds specifically to a site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay." Zavada et al. (WO 95/34650) do not disclose or suggest that the MN protein is involved in cell adhesion. Neither do Zavada et al. (WO 95/34650) disclose or suggest that the use of a cell adhesion assay would be advantageous for "identifying an organic or inorganic molecule that binds specifically to a site on a MN protein, to which

vertebrate cells adhere in a cell adhesion assay," as required by the claim.

Applicants respectfully submit that the instant claims are based on the discovery that the MN protein is a cell-adhesion molecule (CAM). In contrast, the only reference in Zavada *et al.* (WO 95/34650) to MN expression possibly being related to intercellular communication or cell adhesion is on page 70, lines 11-13 which states: "MN expression is most often localized on the cellular plasma membrane of tumor cells and may play a role in intercellular communication or cell adhesion." [Emphasis added.] Without the knowledge that the MN protein functions as a CAM, Zavada *et al.* (WO 95/34650) cannot disclose or suggest the claimed methods of "identifying an organic or inorganic molecule that binds specifically to a site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay."

Applicants respectfully conclude that WO 95/34650 does not anticipate the invention as claimed and that the rejection has been overcome. Applicants respectfully request that the Examiner reconsider and withdraw this 102 rejection in view of the above remarks.

35 U.S.C. Section 102 Rejection

Claims 31-32, 34-42 stand "rejected under 35 U.S.C. 102(e) as being anticipated by Zavada *et al* (US Patent No. 6,297,051)." [Office Action, page 5, Section 14.] In addition,

the Office Action states, "Zavada *et al* teach the identification of peptides that bind to the MN protein within the sequences represented by SEQ ID No:10, 97-106 and 107-108 and 137-138. Furthermore, Zavada *et al* teach that such peptides are used in the inhibition of growth of tumor cells." [Office Action, page 5.]

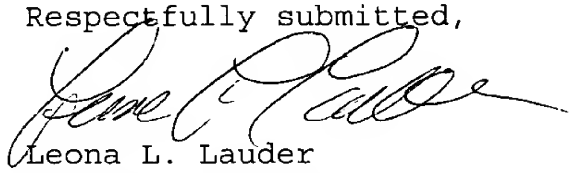
Applicants respectfully traverse this rejection and point out that the cited reference is not prior art to the instant claims. The present application claims priority from U.S. Application No. 09/177,776, which has since issued as the cited U.S. Patent No. 6,297,051. Therefore, Applicants respectfully submit that the rejections have been overcome and request the withdrawal of the rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claim amendments be entered and that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the

subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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